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	Patents ADP number *(if you know it)*	5830122002
	If the applicant is a corporate body, give the country/state of its incorporation	Netherlands Antilles
4.	Title of the invention	PHOSPHOLIPID COMPOSITIONS
5.	Name of your agent *(if you have one)*	COLE Paul Gilbert
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	Lucas & Co 135 Westhall Road Warlingham Surrey CR6 9HJ
	Patents ADP number *(if you know it)*	05815709001

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PHOSPHOLIPID COMPOSITIONS

Field of the invention

The present invention relates to the formation of stable, solid or powdered lipid compositions generally. It particularly relates to lipid compositions containing both lipophilic and hydrophilic compounds for administration to a living organism. Specifically, it describes the preparation of novel lipid compositions in solid compact and particulate forms that have improved physical characteristics and higher loading capacity for biologically active compounds. More specifically, it relates to stable compositions with superior bioavailability, suitable for oral and other applications.

Background to the invention

A major problem in delivering biologically active compounds concern poor absorption which may be due to (i) low solubility in aqueous media, and (ii) poor membrane permeability. These adversely affect bioavailability and reduce efficacy. The problem applies in particular to lipophilic compounds and presents a difficult challenge, particularly to the pharmaceutical industry, from both technical and commercial perspectives. Commercially, the inability to improve bioavailability may be costly if the time to market approval is either delayed significantly or prevented. Indeed, numerous compounds which possess promising pharmacological activity are abandoned in the late stages of development because of poor and erratic bioavailability. In some instances it may be possible to improve bioavailability by forming a derivative that is more hydrophilic without unacceptable changes in pharmacokinetics.

It is difficult to find a carrier system that solubilises and improves the bioavailability of lipophilic compounds, that is efficient and non-toxic for oral administration and that is easy to produce in stable solid forms. Ethanol and ethoxylated surfactants are widely employed in liquid compositions although there are serious limitations in their use. Another approach is to have the active material in a colloidal form or as a co-precipitate with the aim of improving dissolution

characteristics. However, this may not completely solve the problem because the amount of material dissolved and its low membrane permeability may still defy efforts to improve bioavailability.

Problems of poor bioavailability are not limited to hydrophobic compounds. Some hydrophilic compounds with large molecular weights may give similar problems. Examples of hydrophilic compounds which are poorly absorbed include peptides e.g. insulin, peptidomimetic compounds, and genetic material e.g. oligosense nucleotides, etc. Poor bioavailabity in these compounds may be due to low membrane potential rather than solubility.

The benefits in using micelle and bilayer forming lipids, particularly membrane lipids e.g. phospholipids as carriers are well known. Phospholipids are the major component of liposomes which are microscopic vesicles for carrying biologically active compounds. In this specification *lipid* refers to both micelle and bilayer forming lipids. The definition also includes glycolipids, ceramides, gangliosides and cerebrosides. Preferred micelle and bilayer forming lipids are membrane lipids e.g. phospholipids but may also include other polar lipids and derivatives of polar lipids. *Biologically Active Compounds* are substances that have a physiological or pharmacological effect in a living organism. *Lipid associates* are aggregate structures formed between the lipid, active compound and one or more hydrophilic polymers. The compound may be either in molecular association or suspended inside the lipid-polymer associates. Alternatively, it may simply be in uniform dispersion in admixture with the lipid polymer associates. Lipid associates may be particulate with mean diameters between e.g. about 1mm to 5mm or they may be solid compacts.

Co-pending application PCT/GB98/01803 describes a lipid composition comprising at least one micelle forming lipid eg monoacyl phospholipid and mixtures of monoacyl and diacyl phospholipids that are effective in carrying lipophilic

compounds in molecular form. The compositions may be a waxy solid, a paste-like material or a viscous fluid suitable for filling into hard or soft gelatine capsules.

The preparation of lipid-drug co-precipitates using diacyl phospholipids to increase the dissolution behaviour of poorly water soluble drug solvates, and the possibility of modifying drug release from such dispersions by incorporating small amounts of polyvinyl pyrollidone has been described in J. *Pharm. Sci.* 81, 283-286 (1992). The compositions were prepared essentially by co-precipitation and resulted in the incorporation of lipid in the crystalline structure of the solvate. The residual solvent trapped in the solvate was given as a possible reason for the improved solubility of the poorly water soluble compound.

PCT/US86/00637 discloses the use of non-esterified fatty acids and monoglycerides together with minor amounts of a monoacyl lipid (lyso phosphatidylcholine) to form lipid particles which show improved oral absorption for various lipophilic compounds. Improved oral absorption is claimed to be due to the unique properties of the mixture.

Enhanced bioavailability of hydrophilic molecules has also been reported using medium chain triglycerides in W/O micro emulsions, see *Proceed. Intern Symp. Control. Rel. Bioact. Mater., 22* (1995).

The use of enzyme modified lecithin containing both monoacyl and diacyl phospholipids as emulsifiers is well known. These phospholipid containing compounds are widely employed to stabilise dispersed phase systems particularly in food technology, but have not previously been used widely as carriers for biologically active compounds.

The prior art concerning monoacyl phospholipids mainly describes the property of micellar solutions to disrupt membranes. EP-B-O 256 090 claims the use of a specific monoacyl lipid i.e. lyso-phosphatidylethanolamine alone or in combination

with other diacyl phospholipids to solubilise hydrophobic materials in small unilamellar vesicles (SUVs) suspensions. As far as the applicants are aware there has been no prior disclosure on monoacyl phospholipids, particularly in the form of enzyme modified lecithin containing hydrolysed phospholipids with *GRAS* status to form firstly lipid associates with biologically active compounds in solid compositions and secondly to improve oral bioavailability.

Summary of the invention

This invention is concerned with an alternative method through the formation of associate structures comprising the active moiety, lipid and hydrophilic polymer, to deliver biologically active compounds more effectively.

In another aspect, the invention is also concerned with the formation of solid lipid compositions comprising lipids which are difficult to process and employ in solid forms because of their soft, waxy nature.

The invention provides substantially anhydrous solid lipid compositions for improving the handling and processing qualities of waxy lipid substances. Surprisingly, the compositions further improve the solubility and/or bioavailability of biologically active compounds. The compositions are non-liquid forms and are also easy to prepare. They may be solid compacts or they may be particulate, comprising at least one polar monoacyl lipid derivative or at least one diacyl derivative, preferably combination mixtures of polar monoacyl and diacyl lipid derivatives in association with the active compound. Essentially, at least one solid hydrophilic substance, most prefcrably a polymer, is included in the compositions to form lipid associates of sufficient hardness and physical characteristics to turn waxy lipids into particulate forms and/or compacts. Although particle size is not a limitation, the mean particle diameter of the solid lipid associates is preferably between about 1mm to 5mm. At least one biologically active compound may be present in the lipid associate. The active compound may be added to the solution or suspension of lipid and polymer

before removal of solvent or hydrophilic medium or it may be blended into the powdered lipid polymer associates after drying. In this case, the active compound forms associates with the lipid polymer *in situ* upon hydration. Alternatively, the composition may be a mixture of e.g. two or more lipid associates that contain different active compounds. Incompatible substances or compounds that work better when used in combination can be kept apart. Separation of active compounds in this manner within the same dosage form would not be possible in liquid compositions.

The dried compositions comprising lipid and polymer have the potential to swell in water or other aqueous medium to form viscous intermediate compositions. Hydration may be performed extemporaneously prior to use in water or aqueous media, or it may take place *in situ* e.g. inside a capsule or tablet in the GI tract. The hydrated structures may further disperse and reassemble in water or other aqueous media and form aqueous suspensions of smaller lipid particles. Release of the active compound into an aqueous milieu may take place either from the hydrated gel-like structure or from the aqueous suspension of discrete lipid aggregates.

Polymers modify the physical characteristics e.g. hardness of a soft or waxy lipid and affect the formation of intermediate structures on hydration and facilitate further conversion of these structures to microscopic lipid suspensions in water or other aqueous medium. Biologically active compounds are found to have extremely high association in the anhydrous solid forms, the hydrated structures and where appropriate, the resultant aqueous dispersions. Unexpectedly, polymers also improve the association between the lipid and the active compound and almost 100% association between the lipid and the biologically active compound may be possible. They may improve chemical and physical stability and protect the lipid from oxidative and hydrolytic decomposition.

Description of preferred embodiments

Carrier systems are designed to maximise the performance and improve stability of active compounds. The system must be compatible and deliver the active compound to a target site in a controlled manner. Above all, the components used must be non-toxic and should confirm to set specifications to ensure reproducible performance. Although oral administration is the preferred route of medication, compounds are sometimes delivered via alternative routes e.g. inhalation, parenteral, transdermal. These portals can however create problems and are generally only considered when GI absorption is inadequate or cannot be sufficiently controlled. An efficient oral delivery system may provide the key to unlocking the clinical potential of problem compounds in drug discovery programmes. By improving the bioavailability or controlling the release of potent drugs, toxicity may also be reduced because of the smaller doses that need to be given. For compounds that are expensive or available only in small quantities, it is an important consideration. The importance of delivery systems is widely recognised and the quest to improve and control bioavailability of problem drugs is one of the most active pursuits in pharmaceutical research.

An object of the present invention is to provide an improved carrier for hydrophilic and particularly for hydrophobic compounds that is versatile, safe, efficient and cost effective. It is a further object of the invention to modify lipid components that are normally soft or waxy substances so that they can be powdered and filled into hard gelatine capsules or the like. Alternatively, they may be compacted into solid forms e.g. tablets. Lipids are generally not suitable for processing into solid forms except when used in small amounts or when extruded or moulded. This is one reason that lipids, particularly phospholipids, are not used more widely as carriers.

The present invention provides for compositions in compact and/or particulate forms, comprising at least one micelle forming monoacyl lipid and/or at least one bilayer forming diacyl lipid preferably in association with an active compound in a

solid matrix which also comprises at least one polymeric material. The polymer may typically comprise about 50% by weight of the composition. However, this is not a strict requirement and in some cases, particularly when substantively hard and compactable compositions are preferred, 95% or more by weight of the polymer/s may be used. The active compound may be suspended as lipid associated particles in the lipid polymer or preferably, substantially in homogeneous molecular association as a solid solution. The polymer/s is normally added as a solution in an organic solvent or hydrophilic medium and the solid lipid associate is formed after solvent removal. In cases where the polymer is water soluble, the solvent may be water. The solid lipid associate may be further processed into fine powders, granules, micro-pellets and micro-spheres for filling into capsules. Alternatively the granules may be compacted into e.g. tablets, lozenges, troches, buccal or mucosal tablets, pessaries, etc.

The inclusion of hydrophilic polymer/s in the lipid associates confer a number of important benefits to the composition. Firstly, the lipid is converted into friable compositions that are comminutable at ambient temperatures to free flowing powders or processed into granules. Secondly, the lipid associates have improved association for active compounds. Thirdly, solid lipid associates are stable and can tolerate substantial amounts of water without adversely affecting physical characteristics. Lastly, the solid lipid associates have the potential to swell and form gel-like structures. The hydrated intermediate structures act as a bulk reservoir for controlling drug release and may further form suspensions of discrete lipid aggregates in large excess of water or aqueous medium *in situ*.

The powdered lipid associates may be filled into hard capsules or they may be processed into granules for tabletting with the aid of suitable excipients. These dosage forms may be used e.g. in pharmaceutical, dietetic, food, toiletry, cosmetic, veterinary, aquaculture, horticulture and other industrial applications, or where there is need to improve the solubility of poorly water soluble compounds and/or enhance or control absorption of both water and oil soluble substances.

Lipids and Lipid Blends

In most cases, either the monoacyl or diacyl polar lipid can be used on its own to improve bioavailability with an active compound by forming molecular associates. Preferred compositions are however, compacts or particulate associates comprising at least one monoacyl lipid component. Most preferred compositions are lipid associates with mixtures of at least one monoacyl and at least one diacyl polar lipid. Although in most cases, it is preferred to have the active compound in molecular association with the polar lipids, compositions containing monoacyl phospholipid, diacyl phospholipid and hydrophilic polymer may also improve bioavailability even though the active compound is present as colloidal particles. As a general rule, lipophilic compounds are mostly in solid molecular solution, whereas hydrophilic compounds may be in particulate dispersion in the lipid polymer matrix.

The monoacyl lipid(s) is preferably the monoacyl derivative of a phospholipid, but it can also be the monoacyl derivative(s) of glycolipids or sphingolipids. Other suitable micelle forming polar lipid derivatives and fatty acid esters may also be used. The lipids may be derived from natural plant, or animal or microbiological sources, synthesised or partially synthesised including polyethyleneglycol (PEG) derived monoacyl phospholipids, eg. pegalated monoacyl phosphatidyl ethanolamine.

The diacyl lipid(s) is preferably a phospholipid but may also be other polar lipids or fatty acid esters. Examples of phospholipids are phosphatidylcholine, phosphotidylethanolamine, phosphatidylglycerol, phosphatidylinositol, phosphatidylserine and sphingomylin. The acyl chain can either be unsaturated or saturated and can have between 12 to 22, preferably 14 to 18 carbon atoms. Other membrane lipids such as glycolipids, ceramides, gangliosides and cerebrosides can be used in place of, or partial place of, phospholipids.

Although the lipid composition may comprise entirely of at least one monoacyl or diacyl lipid component on its own, preferably the weight ratio of diacyl to

monoacyl lipid or other micelle forming lipid in the mixture would normally be from 1:99 to 99:1, preferably between 1:25 and 25:1 and most preferably 1:10 and 10:1.

In the case of phospholipids, instead of mixing pure fractions of the two lipids to obtain the target ratios, partially enzyme hydrolysed mixtures of lecithin that have the required proportions of the monoacyl to diacyl lipid components are preferred. These phospholipid mixtures, which are known as enzyme modified lecithins are freely permitted in foods without restrictions and should thus present no problems for oral use. Wherever possible hydrolysed lecithin containing from 10 to 80 preferably 60 to 80 mole percent of monoacyl phospholipids obtained by enzyme hydrolysis with e.g. phospholipase A2 is preferred. The lecithin should be substantially pure and substantially free from non polar lipids. Preferably the lecithin is GMO free or does not contain detectable levels of genetically modified components. Mixtures of phospholipids with other polar lipids may also be used in some cases.

Lipid : Active Ratios

The quantity of lipid employed to form the associate depends on a number of considerations. These include the amount of active compound present, solubility, bioavailability and related formulation requirements. Where the invention is required to substantially carry active compounds in molecular association, higher amounts of lipid may be required to form the associates. Lipid: active compound ratios of 99:1 or even more may be employed in the case of extremely potent compounds or strongly hydrophobic problem drugs. In most cases, lipid: active ratios between 25:1 to 1:25 would be sufficient. Usually ratios between 20:1 to 1:5 would be quite sufficient to (i) substantially solubilise lipophilic compounds or (ii) improve the bioavailibilty of both lipophilic and hydrophilic compounds by increasing membrane permeability and controlling release.

Generally, less lipid is required to solubilise lipophilic compounds if higher proportions of monoacyl components are present, reducing the total amount of lipid in

the composition. This is also generally the case where the active compound is hydrophilic and the lipid polymer composition is used mainly to control hydration and improve bioavailability at the site of absorption. Where the active compound is substantially dispersed as discrete particles in the lipid polymer matrix, they should be less than 1μm and be preferably below 250 nm in mean diameter.

Polymer

The compositions contain one or more polymer dispersible or soluble in water or an organic solvent. Water miscible solvents e.g. C2 - C6 alcohols, esters or ketones are preferred, although other solvents that are non water miscible may also be used to disperse or dissolve the polymer. The amount of polymer employed may lie between 5% and 95% by weight based on the weight of the composition, typically between 20 and 80%, depending on the required hardness and control over hydration characteristics of the lipid polymer matrix. Normally, higher amounts of polymer produce compositions that are harder and easier to turn into powders and granules and for compaction into tablets or the like. The compositions particularly in the form of a solid compact, also tend to take a longer time to hydrate and swell and are therefore more suitable for retention at a particular site. Water insoluble polymers may be dissolved or hydrated in an organic solvent e.g. ethanol, together with the lipid and the active compound to form a homogeneous solution or dispersion in the first instance. In other cases where water soluble polymers are used, they are dissolved/hydrated separately before adding to the organic lipid solution. Removal of the hydrophilic medium results in an anhydrous or nearly anhydrous solid lipid polymer association structure sufficiently hard to be micronised or turned into granules suitable for compaction e.g. tablets. Alternatively, during removal of the hydrophilic medium, the composition may be spheronised or pelletised with or without the aid of excipients. Removal of the hydrophilic medium may be carried out by any suitable method including spray drying and lyophilisation. Polymers allow natural unsaturated phospholipids in particular with low phase transition temperatures that are characteristically soft waxes at room temperature to be more easily handled. The solid

compositions formed have good long term ambient temperature and elevated temperature storage properties. They also allow large amounts of phospholipid to be used as delivery vehicles. Use of time dependent polymers (i.e. polymers that swell at a steady rate depending on time and relatively independent of pH) with different swelling properties modifies hydration of the lipid associates in aqueous environment and offer a method to control and prolong the release of active compounds aalong the GI tract independent of pH. Protection against hydrolysis and breakdown of the lipid in a low pH aqueous environment is also possible when the polymer used is insoluble in acid medium, allowing the active compound to be released e.g. lower down in the GI tract. Storage stability of aqueous suspensions of the lipid associates when it is suspended in buffered solution is also much improved.

Preferred polymers for hardening lipid are the natural gums and derivatives, e.g. sodium alginate. They may also be synthetic polymers e.g. methacrylic polymers and copolymers, carboxy vinyl polymers and copolymers. Gelatin or partially hydrolysed gelatin may also be used. Most preferred polymers are the celluloses e.g. carboxymethyl cellulose, ethyl cellulose and combinations of cellulose with alginates or methacrylic polymers, and starches and modified starches e.g. maize starch, phosphated starch, hydroxypropylated starch and starch sodium octenylsuccinate, etc.

Generally, two requirements seem to apply although the invention does not depend entirely on these postulates, as there may be other reasons.

1. Charged polymers significantly increased lipid hardness.

Some of the best lipid-hardening polymers have negatively charged carboxyl groups (such as sodium alginate and Eudragit L100 - methacrylic acid copolymer) or negatively charged sulphate ester groups (such as carrageenan).

2. The polymers should be substantially dissolved or dispersed in a suitable solvent or hydrophilic medium.

Polymers should be dissolved or at least dispersed to a colloidal solution before being dried with the lipid to significantly increase hardness. The definition for hydrophilic medium may also extend to sugars in some cases. Indeed, sugars could be

regarded as a 'solid' hydrophilic medium. This may be the reason why combinations of polymers and some sugars are particularly effective in hardening lipid. Amylose, lactitol and xylitol are suitable examples for incorporation in the solid lipid polymer compositions for this purpose. Charged molecules are generally more soluble in aqueous media, rather than organic solutions, and this is why there are more water-soluble polymers that can harden the lipid than ethanol-soluble polymers. Generally, suitable lipid-hardening polymers that are ethanol-soluble are also soluble in aqueous media as well, at appropriate pH.

Table 1 summarises the charge found on a number of common pharmaceutical polymers.

Table 1. Charge characteristics of a number of natural polysaccharide and synthetic polymers commonly used in the pharmaceutical industry.

Polymer	Charge	Ionic Group
Sodium carboxymethylcellulose (Carmellose sodium)	Acidic or anionic	Carboxyl
Alginic acid	Acidic or anionic	Carboxyl
Sodium alginate	Acidic or anionic	Carboxyl
Modified starches	Acidic or anionic	Carboxyl
Agar	Acidic or anionic	Sulphate Ester
Carrageenan	Acidic or anionic	Sulphate Ester
Gum arabic (Acacia)	Acidic or anionic	Carboxyl
Gum tragacanth	Acidic or anionic	Carboxyl
Gum xanthan	Acidic or anionic	Carboxyl
Pectin	Acidic or anionic	Carboxyl
Carboxypolymethylene (Carbomer)	Acidic or anionic	Carboxyl
Methyl Vinyl Ether / Maleic Acid Copolymer	Acidic or anionic	Carboxyl
Methacrylic Acid Copolymer	Acidic or anionic	Carboxyl
Ammonio Methacrylate Copolymer	Ionic Salt	Amino-chloride Salt
Basic Polymethacrylate	Basic or cationic	Amino
Chitosan	Basic or cationic	Amino
Starch	Neutral or nonionic	/
Hydroxyethylcellulose	Neutral or nonionic	/
Hydroxypropylcellulose	Neutral or nonionic	/
Hydroxypropylmethylcellulose (Hypromellose)	Neutral or nonionic	/
Gum guar	Neutral or nonionic	/
Carob bean Gum (Ceratonia)	Neutral or nonionic	/
Poly(vinyl alcohol)	Neutral or nonionic	/
Poly(vinylpyrrolidone) (Povidone)	Neutral or nonionic	/
Poly(oxyethylene glycols) (Macrogols)	Neutral or nonionic	/
Poly(oxypropylene) poly(oxyethylene) block copolymer (Poloxamer)	Neutral or nonionic	/

An important contribution made by the inclusion of polymers in the solid lipid compositions is that it provides a solid lipid composition which is tolerant to relatively

large amounts of residual, adsorbed or deliberately added water without significant deterioration or changes in its physical properties such as flow properties, friability and softness.

Most of the natural polysaccharide polymers, starches and their derivatives, cellulose polymers and gelatines are pharmaceutically acceptable for oral, mucosal and topical administration. From their widespread use in food, they are not considered to represent a hazard to health.

Table 2 summarises the physical characteristics and lipid hardening properties of some of the pharmaceutical polymers. It must be clearly understood that this is not an exhaustive list and other hydrophilic polymers not included in this list may also be suitable. Combinations of polymers, e.g. mixtures of alginate with celluloses may be preferred in certain compositions to obtain the required hardness and physical characteristics. In addition, any suitable method of mixing and solvent removal can be employed to produce solid lipid polymer compositions on a commercial scale.

Table 2 Examples of polymers that may be suitable for forming lipid polymer solids
Characteristics of some pharmaceutical polymers, used in lipid polymer formulations.

Polymer	Polymer Charge	Solvent Solubility	Lipid Hardening Properties	Reason For Lipid Hardening Properties
Sodium carboxymethylcellulose (Carmellose sodium)	Acidic or anionic	Dispersible in water Insoluble in ethanol	Very good, solid hard and dry	Carboxyl group on derivatised glucose monomers.
Sodium alginate	Acidic or anionic	Soluble in water Insoluble in ethanol	Very good, solid hard and dry	Carboxyl group on guluronic acid and mannuronic acid monomers
Modified Starch	Acidic or anionic	Swellable in water	Very good, solid hard and dry	Carboxyl group
Agar	Acidic or anionic	Soluble in hot water Insoluble in ethanol	Very good, solid hard and dry	Sulphated agarose and agarpectin polymers with carboxyl groups on the glucuronic acid monomers of agarpectin
Carrageenan	Acidic or anionic	Soluble in hot water Insoluble in ethanol	Very good, solid hard and dry	Sulphated galactose and anhydrogalactose monomers
Gum arabic (Acacia)	Acidic or anionic	Soluble in water Insoluble in ethanol	Good, solid hard and dry	Carboxyl group on glucuronic acid monomers
Gum tragacanth	Acidic or anionic	Soluble in water Insoluble in ethanol	Very good, solid hard and dry	Carboxy group on galacturonic acid monomers
Gum xanthan	Acidic or anionic	Soluble in water Insoluble in ethanol	Very good, solid hard and dry	Carboxyl group on glucuronic acid monomers
Pectin	Acidic or anionic	Soluble in water Insoluble in ethanol	Very good, solid hard and dry	Carboxy group on galacturonic acid monomers
Carboxypolymethylene (Carbomer)	Acidic or anionic	Soluble in water Soluble in ethanol	Very good, solid hard and dry	Carboxyl groups on synthetic polymer
Methyl Vinyl Ether / Maleic Acid Copolymer (Gantrez S)	Acidic or anionic	Soluble in water Soluble in ethanol	Very good, solid hard and dry	Carboxyl groups on synthetic polymer
Methacrylic Acid Copolymer (Eudragit L&S)	Acidic or anionic	Soluble in aqueous media > pH7 Soluble in ethanol	Excellent, solid hard, crispy and dry	Carboxyl groups on synthetic polymer
Ammonio Methacrylate Copolymer (Eudragit RL &RS)	Ionic Salt	Permeable in water Soluble in ethanol	Very good, solid hard and dry	Amino-chloride salt
Basic Polymethacrylate (Eudragit E)	Basic or cationic	Soluble in aqueous media < pH5 Soluble in ethanol	Very good, solid hard and dry	Amino groups on synthetic polymer
Chitosan	Basic or cationic	Soluble in aqueous media at very low pH Insoluble in ethanol	Very good, solid hard and dry	Amino group on derivatised glucose monomers
Starch	Neutral or nonionic	Swellable in hot water	Moderate	NA
Hydroxyethylcellulose	Neutral or nonionic	Soluble in water Insoluble in ethanol	Moderate	NA
Hydroxypropylcellulose	Neutral or nonionic	Soluble in water Soluble in ethanol	Moderate	NA
Hydroxypropylmethylcellulose (Hypromellose)	Neutral or nonionic	Soluble in water Insoluble in ethanol	Moderate	NA
Gum guar	Neutral or nonionic	Soluble in water Insoluble in ethanol	Moderate	NA
Carob bean Gum (Ceratonia)	Neutral or nonionic	Soluble in water Insoluble in ethanol	Moderate	NA
Poly(vinyl alcohol)	Neutral or nonionic	Soluble in water Insoluble in ethanol	Moderate	NA
Poly(vinylpyrrolidone) (Povidone)	Neutral or nonionic	Soluble in water Soluble in ethanol	Good,	Nitrogen atom of cyclic amide may form weak electrostatic interactions

Biologically Active Compound

The composition may further comprise a biologically active compound which has lipophilic and/or hydrophilic properties. Preferably, it is in solution in the composition but it may also be in dispersion.

Examples of biologically active lipophilic compounds include hydrophobic neutral cyclic peptides eg. cyclosporin A, taxol, tacrolimus or a macrolide e.g. a rapamycin, and derivatives thereof. Examples of hydrophilic biologically active compounds are insulin, calcitonin and heparin.Another unrelated group of compounds which may be used with advantage are antioxidants, e.g. ubiquinone, tocopherols, carotenoids, and bioflavonoids. Other examples of therapeutic classes of compound, members of which may be carried in the invention to improve delivery are given below.

Antibiotics, antidepressants, antidiabetics, anti-epileptics, antifungals, anti-gout, antihistamines, anti-malarials, antimigraines, antimuscarinics, anti-neoplastics, anti obesity agents, antiprotozoals, antipyretics, antisense oligonucleotides, anti-virals, anxiolytic, sedatives, hypnotics and anti-psychotics, haemostatics, calcium regulating agents, cardiovascular, chelating agents antidotes, contrast media, corticosteroids, cough supressants/expectorants and mucolytics, dermatological agents, diagnostic agents, disinfectants and preservatives, dopaminergic agents, GI agents, general anaesthetics, genetic material, hypothalmic and pituitary hormones, lipid regulating agents, local anaesthetics, nucleotides, nutritional agents and vitamins, parasympathomimetics, peptides, polypeptides, peptidomimetics, proteins, prophylactic anti-asthma agents, prostaglandins, radio pharmaceuticals, resistance modifying agents, immunosuppressants, sex hormones, skeletal muscle relaxants, stimulants/anorectics, sympathomimetics, vaccines, immunoglobulins and antisera, xanthines.

The amount and concentration of active compound in the composition depends on the type of application and is not a limiting feature of the invention.

The invention is now described in the following typical examples. The examples illustrate the effect of varying the lipid and polymers on the formation and properties of the solid lipid associates. They also show the use of different lipid and polymers with and without biologically active compounds to obtain solid particulate lipid associates that may be used as such as powders or granules, filled into hard

gelatin capsules or the like, or compacted into e.g. tablets or the like. It must be clearly understood that the active compounds shown are typical examples to illustrate the invention and not to limit the scope of the invention.

Preparation of solid polymer lipid

Method

The solid lipid compositions prepared with active and polymer, were made using the following method. Unless otherwise stated 5g of the dried lipid polymer composition was prepared in each case. Much larger amounts may be prepared by the use of appropriate equipment.

The lipid and active were dissolved in ethanol. The polymer was hydrated in water (or ethanol in the case of acrylic polymers) to obtain a viscous solution. The polymer solution was weighed into a glass jar and the lipid/ethanol/active dispersion was added. The mixture was stirred thoroughly until a homogenous gel formed. The gel was vacuum dried at 50°C/0.1mBar for ~24hours to remove all the ethanol and water.

Lipid Type

Examples 1-4

Solid lipid compositions shown below were prepared following the method described above using two different types of phospholipid which significantly differed in their phosphatidylcholine (PC) and monoacyl phosphatidylcholine (MAPC) contents. It was found that the appearance of the solids was influenced to some extent by the type of lipid used in the formulation. For example VP145 contains about 50% by weight of PC and 5% by weight MAPC, remainder other polar lipids, generally produced darker coloured and slightly softer solids than equivalent formulations prepared with the lipid (VP 200) containing about 60% by weight MAPC and 40% PC.

Examples 1-4

Sample	Dry Excipients	Appearance Before Drying	Appearance After Drying
VP145 lipid, no polymer	VP145/Nystatin (20 : 1)	Dark golden viscous suspension	Dark golden soft wax
VP200 lipid, no polymer	VP200/Nystatin (20 : 1)	Golden viscous suspension	Golden wax
VP145 lipid. sodium alginate polymer	VP145/Nystatin/ManugelLBB (50 : 2.5 : 47.5)	Pale yellow smooth gel	Golden brown crushable solid
VP200 lipid, sodium alginate polymer	VP200/Nystatin/ManugelLBB (50 : 2.5 : 47.5)	Pale yellow smooth gel	Yellow fine flowable powder

Characteristics of solid lipid polymer compositions

After drying at 50°C/0.1mBar the majority of the ethanol and/or water was removed from the compositions to obtain a solid, crushable lipid composition. The solid composition may be powdered or it may be turned into granules with the aid of suitable excipients, for compressing into tablets.

Polymer Type

Examples 5-16

Several different polymers were incorporated in Examples 5-16, with VP145 lipid to try to establish which types of polymers were more suitable for hardening the lipid. The solids were prepared using various concentrations of polymer, either in aqueous media, in ethanol or as a dry powder. The lipid was dispersed in an equal amount of ethanol (w/w) before being added to the polymer.

Examples 5 - 16

Sample	Dry Ratio	Appearance Before Drying	Appearance After Drying
No polymer	VP145	Golden runny liquid	Golden wax
Gum Arabic (5.3% in water)	VP145/Acacia (70 : 30)	Light brown gel	Golden slightly hard dry solid
Gum Xanthan (2% in water)	VP145/XanthanFN (70 : 30)	Pale golden smooth gel	Light golden crispy hard solid
Carrageenan (1.5% in water)	VP145/GelcarinGP379N (70 : 30)	Pale golden smooth gel	Light golden crispy hard solid
Methyl Vinyl Ether/Maleic Acid Copolymer (12% in water)	VP145/ GantrezS-97BF (70 : 30)	Pale golden smooth gel	Light golden crispy hard solid

Polyvinyl Alcohol (6% in water)	VP145/PVA (70 : 30)	Pale golden gel with some insoluble polymer residues	Golden slightly waxy solid
Hydroxyethylcellulose (5% in water)	VP145/Natrosol250Gpharm (70 : 30)	Golden opaque gel	Golden slightly waxy solid
Hydroxypropylcellulose (6% in water)	VP145/KlucelGFEP (70 : 30)	Golden opaque gel	Golden slightly waxy solid
Hydroxypropylcellulose (2% in ethanol)	VP145/KlucelGFEP (70 : 30)	Golden thick liquid	Golden slightly waxy solid
Sodium Carboxymethyl-cellulose (9% in water)	VP145/Blanose7LF (70 : 30)	Golden opaque gel	Golden yellow hard solid flakes
Sodium Carboxymethyl-cellulose (Dry powder)	VP145/Blanose7LF (70 : 30)	Golden liquid with insoluble white particles	Golden waxy solid with white particles
Starch (Dry powder)	VP145/Starch (70 : 30)	Golden liquid with insoluble small white particles	Golden waxy solid with small white particles

The charge density on the polymer also influenced the hardness of the lipid. Gum arabic polymer, for example, consists of monomers of L-arabinose, D-galactose, L-rhamanose and D-glucuronic acid, in the approximate ratio of 3:3:1:1. Since only the glucuronic acid monomer is charged, the polymer has a low charge density and had only average lipid-hardening properties. Sodium alginate, on the other hand, consists of D-mannuronic acid and L-guluronic acid monomers, both of which are charged. This polymer has a high charge density and had very good lipid-hardening properties. Furthermore, the advantage of using combinations of two or more polymers is not ruled out and may be preferred in some cases.

Polymer Grade

Examples 17-19

Solid lipid compositions were prepared with various grades of the same polymer according to the previous examples, to see how the grade affected the hardness of the final formulation. The solids were prepared using a 4% aqueous solution of polymer and incorporated VP200 lipid and Cyclosporin A active in a ratio of 5:1. It was found that the appearance after drying was not significantly influenced by the grade of polymer. In the case of compositions prepared with sodium alginate, both high and low viscosity Keltone (Monsanto) produced similar solids.

Examples 17-19

Sample	Dry Excipients	Appearance Before Drying	Appearance After Drying
No polymer	VP200/CyA (5 : 1)	Golden viscous liquid	Yellow wax
20% Sodium Alginate Prepared with high viscosity polymer	VP200/CyA/KeltoneHVCR (66.67 : 13.33 : 20)	Pale yellow smooth gel	Yellow hard crushable solid
20% Sodium Alginate Prepared with low viscosity polymer	VP200/CyA/KeltoneLVCR (66.67 : 13.33 : 20)	Pale yellow smooth runny gel	Yellow hard crushable solid

Polymer Concentration

Examples 20 - 26

Lipid sodium alginate solids were prepared with various aqueous concentrations of sodium alginate polymer in Examples 20 - 26 below. The solids were prepared using a 2%, 4% or a 6% Keltone LVCR polymer solution and incorporated VP805 lipid and Cyclosporin A active in a ratio of 5:1. The lipid and active were dispersed in an equal amount of ethanol (w/w) before being added to the aqueous polymer solution. Polymers were dissolved in water to different concentrations to see if the amount of water in the lipid-polymer formulation affected the final appearance of the lipid polymer solid. It was found that the appearance of the composition was not significantly influenced by polymer concentration. In practice, it was found that using the processing and drying methods adopted, a minimum amount of about 10% by weight of at least one polymer, based on the total weight of the solid composition, was required to substantially harden the soft lipid. It is possible smaller amounts of polymer could be used if blends of polymers and more efficient high shear mixing methods are employed. High shear mixing, for example would allow the use of less water to give a homogeneous composition prior to water removal. Furthermore, hot air or vacuum assisted drying methods would be more efficient in reducing the processing time and reducing residual water content to give stable and harder solid lipid compositions. However, it must be emphasised that the invention produces stable compositions that can tolerate high amounts of residual water without adversely affecting physical characteristics. Thus it may not be necessary to remove water

entirely from the compositions. Any suitable method for drying and removal of solvent may be employed, including but not limited to e.g. fluidised bed drying, spray drying, freeze drying, supercritical fluid extraction, or a combination thereof. Depending on the method of drying employed a solid cake or a powdered composition may be obtained.

Examples 20-26

Sample	Dry Excipients	Appearance Before Drying	Appearance After Drying
No polymer	VP200/CyA (83.33 : 16.67)	Golden viscous liquid	Yellow wax
20% Sodium Alginate Prepared with 6% Polymer	VP200/CyA/SodiumAlginate (66.67 : 13.33 : 20)	Pale yellow gel	Yellow hard crushable solid
20% Sodium Alginate Prepared with 4% Polymer	VP200/CyA/SodiumAlginate (66.67 : 13.33 : 20)	Pale yellow smooth runny gel	Yellow hard crushable solid
20% Sodium Alginate Prepared with 2% Polymer	VP200/CyA/SodiumAlginate (66.67 : 13.33 : 20)	Pale yellow thick liquid	Yellow hard crushable solid
30% Sodium Alginate Prepared with 6% Polymer	VP200/CyA/SodiumAlginate (58.33 : 11.67 : 30)	Pale yellow smooth gel	Yellow hard crispy/flakey crushable solid
30% Sodium Alginate Prepared with 4% Polymer	VP200/CyA/SodiumAlginate (58.33 : 11.67 : 30)	Pale yellow smooth runny gel	Yellow hard crispy/flakey crushable solid
30% Sodium Alginate Prepared with 2% Polymer	VP200/CyA/SodiumAlginate (58.33 : 11.67 : 30)	Pale yellow thick liquid	Yellow hard crispy/flakey crushable solid

Examples 27-29

Solid lipid polymers were also prepared with VP145 lipid and Nystatin active in a ratio of 20 : 1. The lipid and active were dispersed in an equal amount of ethanol (w/w) before being added to the aqueous polymer solution .

Examples 27-29

Sample	Dry Excipients	Appearance Before Drying	Appearance After Drying
No polymer	VP145/Nystatin (20 : 1)	Golden viscous liquid	Yellow waxy solid
47.5% Sodium Alginate Prepared with 12% Polymer	VP145/Nystatin/ManugelLBB (50 : 2.5 : 47.5)	Pale yellow gel	Golden hard crushable solid
47.5% Sodium Alginate Prepared with 6% Polymer	VP145/Nystatin/KeltoneLVCR (50 : 2.5 : 47.5)	Pale yellow runny gel	Golden hard flakes

In principle, there was no maximum limit to how much water could be added to the lipid-polymer formulations before drying as long as the water could be removed on drying. Hence any concentration of polymer could be used. In practice, a minimum

amount of water was necessary to produce a homogeneous hydrated lipid polymer composition that was suitable for drying from a slurry.

Hardness

Examples 30-34

The amount of polymer in the formulations below was varied to see how this affected the final hardness of the solid. The solids were prepared using a 4% or a 6% Keltone LVCR polymer solution and incorporated VP200 lipid and Cyclosporin A active in a ratio of 5:1. The lipid and active were dispersed in an equal amount of ethanol (w/w) before being added to the aqueous polymer solution. The solid compositions from Examples 33 and 34 were particularly suitable for powdering and filling into hard gelatine capsules. Each 500mg capsule would contain 50mg of Cyclosporine A.

Examples 30-34

Sample	Excipients	Appearance Before Drying	Appearance After Drying
No polymer	VP200/CyA (83.33 : 16.67)	Golden viscous liquid	Yellow wax
5% Sodium Alginate	VP200/CyA/SodiumAlginate (79.17 : 15.83 : 5)	Pale yellow blobby gel	Yellow slightly waxy solid
10% Sodium Alginate	VP200/CyA/SodiumAlginate (75 : 15 : 10)	Pale yellow blobby gel	Yellow dry solid with a slight shine - can be broken up
20% Sodium Alginate	VP200/CyA/SodiumAlginate (66.67 : 13.33 : 20)	Slightly blobby creamy gel	Yellow hard crispy solid - can be crushed
30% Sodium Alginate	VP200/CyA/SodiumAlginate (58.33 : 11.67 : 30)	Smooth creamy gel	Pale yellow hard crispy solid - can be crushed to flakes

Stability Of Lipid

Short-term stability studies were carried out to assay for degradation of the lipid both during manufacture and on storage of the lipid polymer solids The stability of the lecithin components PC and MAPC were followed by HPLC analysis. During the manufacturing process the lipid was subjected to high temperature hydrolysing conditions for several hours which could easily have hydrolysed the PC initially to MAPC.

It was found that the lipid appeared stable both during manufacture and on storage of the lipid polymer solids.

Association of active in solid lipid polymer compositions

The examples illustrated below were prepared according to the method used in the previous examples. The association of the active with the lipid was determined using analytical filtration. The assay for the actives was carried out by HPLC. The results indicate that near 100% association of the actives in the lipid polymer associates is possible even after up to 3 months storage at elevated temperature.

Examples 35 - 38

Ex.	Composition	Excipients	Association
35	Lipid/CyA/SodiumCMC	VP805/CyA/Blanose 7LF (50:10:40)	Initial - ~100% 1 month 97.2% (4°C), 98.6% (25°C), 98.0% (40°C) 3 months – 98.8% (4°C), 98.5% (25°C), 98.8% (40°C)
36	Lipid/CyA/Eudragit	VP805/CyA/Eudragit L100 (50:10:40)	Initial - ~100% 1 month – 97.9% (4°C), 97.2% (25°C), 98.1% (40°C) 3 months – 98.9% (4°C), 99.3% (25°C), 98.5% (40°C
37	Lipid/CyA/Sodium Alginate	VP145/CyA/ManugelLBB (50:2.5:47.5)	Initial – 93.4% 1 month – 101.4% (40°C) 6 weeks – 102.0% (40°C))
38	Lipid/CyA/Sodium Alginate	VP805/CyA/ManugelLBB (50:2.5:47.5)	Initial – 96.2% 1 month – 100.0% (40°C) 6 weeks – 99.7% (40°C)

Activity of lipid polymer solids

The activity of the drugs in the lipid polymer solids was assessed using the nystatin formulation. Nystatin was chosen because its activity could be assessed using simple *in vitro* microbiological assays.

The antifungal properties of the nystatin lipid solids were assessed using a cup-plate diffusion assay. The solids were diluted, in aqueous media to form lipid dispersions, which were compared to equal concentrations of a commercially available nystatin suspension, Nystan® (E. R. Squibb and Sons Ltd.). Tryptone-soya agar plates were used that had been inoculated with *Candida albicans* NCPF 3179 to a final concentration of 10^6 viable cells per ml. Solutions were incubated in 5.5 mm wells for 2 hours at room temperature, followed by 18 hours at 37°C. The zones of growth inhibition of the *Candida albicans* were measured and compared in Figure 1.

The following examples further illustrate the scope and utility of the invention.

Example 39 to 41

Several different starches were incorporated in Examples 39 to 41 with VP200 lipid to illustrate the use of these polymers for hardening the lipid. The solids were prepared using various concentrations of polymer in aqueous media. The lipid was dispersed in water without ethanol, before being added to the polymer in Example 39. In examples 40 and 41, the polymers were dispersed in hot water prior to the addition of VP 200 dissolved in ethanol.

Examples 39 to 41

Sample	Dried Ratio	Appearance Before Drying	Appearance After Drying
Starch sodium octenylsuccinate	VP200/ Starch sodium octenylsuccinate (1:1)	Opaque yellow dispersion	Pale yellow very crispy solid
*N-Lok™	VP200/ modified starch (1:2)	Opaque yellow dispersion	Pale yellow very crispy solid
*Crisp Film™	VP200/ high amylose modified starch (1:3)	Opaque off white dispersion	Yellow crunchy solid

*National Starch and Chemical Company

Examples 39 to 41 are base compositions of solid lipid polymer. The biologically active compound may be added to the solution of lipid and polymer before drying or it may be blended into the dried lipid polymer powder to form a uniform mixture. The compositions could be powdered easily for filling into hard gelatine capsules or they could be processed into granules suitable for tabletting

Examples 42 to 44

Several different grades of gelatin were incorporated in Examples 42 to 44 with deoiled lecithin, which contains a mixture of neutral phospholipids, charged phospholipids and glycolipids, to illustrate the use of polymers generally for hardening a lipid widely used in food applications. The solids were prepared using various concentrations of polymer in aqueous media. The lipid was dispersed in water without ethanol, before addition of the polymer to obtain a viscous dispersion

Examples 42 to 44

Sample	Dried Ratio Deoiled lecithin/Gelatin	Appearance Before Drying	Appearance After Drying
Alkali hydrolysed gelatin Bloom strength 200	1:1	Brown slurry	Crispy film
Acid hydrolysed gelatin Bloom strength 150	1:1	Brown viscous dispersion	Crisp film
Hydrolysed gelatin	1:1	Brown slurry	Crisp, brittle film

In all cases, removal of the water results in crispy compositions that could be further comminuted to obtain free flowing powders or granules. The powdered lipid polymer compositions may be used as such in place of ordinary deoiled lecithin in various applications, or they may be employed to carry active compounds either in molecular association or dispersion with the lipid polymer.

Examples 45 to 49

The following examples further illustrate the utility of the invention in rendering various polar lipids and combinations thereof hard and comminutable to extend their use generally, particularly in oral dosage forms.

In examples 45 to 48 the lipid was initially heated gently on a hot plate and the aqueous polymer solution was added and stirred to produce a homogeneous suspension. Removal of water from the slurry was carried out in a vacuum oven at 50 C until the weight of the composition remained constant. A hard, crushable solid

polymer lipid composition was formed in each case. As in the previous examples, an active compound may be added to the slurry before removal of water or it may be blended into the solid polymer lipid powders after removal of water.

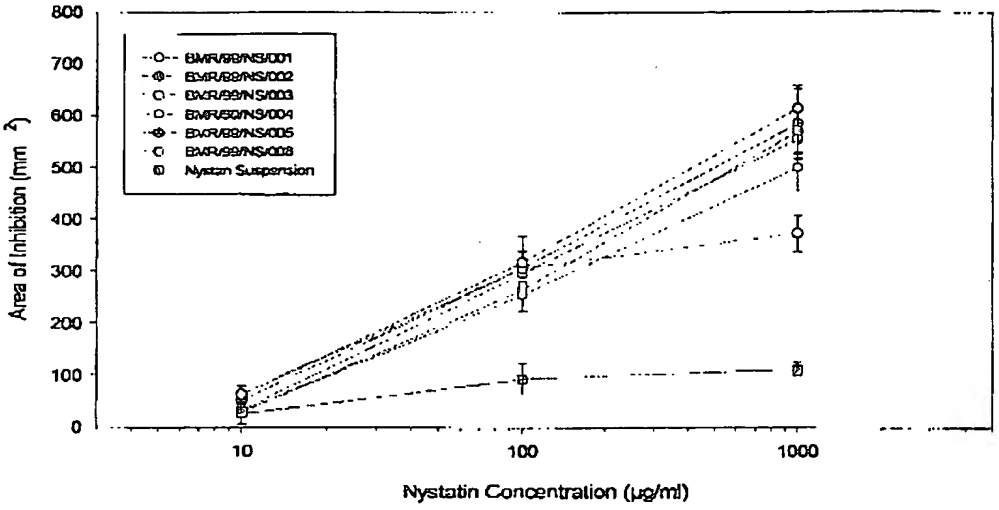
Sample	Dried Ratio Lipid/polymer	Appearance Before Drying	Appearance After Drying
Saccharose monopalmitate	Saccharose monopalmitate/ High amylose maize starch (1:2)	Opaque dispersion	White hard solid composition
PEG 32 glyceryl laurate	PEG 32 glyceryl laurate/ Starch sodium octenylsuccinate (1:2)	Opaque dispersion	Very hard white solid composition
Glyceryl dicocoate	Glyceryl dicocoate/carboxymethyl cellulose (1:2)	Opaque viscous dispersion	Brittle white solid
Saccharose monopalmitate and phosphatidylcholine	Saccharose monopalmitate/ PC/CMC (1:1:2)	Opaque off white viscous slurry	Off white hard composition

Presentation

The waxy nature of lipids has previously prevented the use of effective amounts of lipid in solid dosage forms generally. It is likely that this may be one of the reasons why the use of lecithin in particular for improving drug delivery has not been taken to full advantage. The use of polymers has now been shown to increase the hardness and modified the processing characteristics of lipid. Therefore the potential use for many lipid-based pharmaceutical formulations has increased dramatically.

The lipid polymer formulations have the potential to be incorporated into a number of delivery systems including solutions, suspensions, tablets, capsules, gels, suppositories and pessaries as well as a free powder or granules. The greater potential lies, perhaps, in compressing the powder into a tablet or filling it into a hard gelatin capsule for oral delivery.

Figure 1. Cup-plate diffusion assay of nystatin lipid sodium alginate dispersions, compared to equivalent concentrations of the nystatin suspension, Nystan®.



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